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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/773,476	01/31/2001	Glenn Friedrich	LEX-0126-USA	4146

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EXAMINER	
PARAS JR, PETER	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/773,476	FRIEDRICH ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0701* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's preliminary amendment received on 8/4/03 has been entered. Claims 1 and 7 have been amended. Claims 1-7 are pending.

Election/Restrictions

Applicant's election with traverse of Group 294 in Paper No. 0803 is acknowledged. The traversal is on the ground(s) that the inventions are all related as they are all directed to cells comprising the same construct. This is not found persuasive because it is maintained each of the groups embraces a different nucleotide sequence, each having a different chemical structure, wherein each nucleotide sequence embraced by the claims can encode a different protein. Disruption of nucleotide sequences encoding different proteins in the context of transgenic mice should result in structurally different mice having different phenotypes. Accordingly, the cells of each of Groups 1-341 have different functions and different effects related disruption of different nucleotide sequences. As such the claimed cells comprising disruptions of different nucleotide sequences are different and should be restricted. Also see pages 2-3 of the restriction requirement mailed on 3/27/03. Therefore it is maintained that the inventions are distinct each from the other, each requiring a separate search, for the reasons given above.

The requirement is still deemed proper and is therefore made FINAL.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the

Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-7 as corresponding to Groups 1-293 and 295-341 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 0803.

Drawings

New corrected drawings are required in this application because the drawings are not labeled. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are directed to a genetically engineered mammalian cell comprising a recombinant polynucleotide inserted into a gene comprising the nucleotide sequence *set forth in SEQ ID NO: 294. The claims are further directed to a murine embryonic* stem cell line comprising a retroviral gene trap vector in a gene comprising the nucleotide sequence set forth in SEQ ID NO: 294.

The instant specification has disclosed novel cDNA sequences produced using gene trap technology. See the specification at page 6. The claims embrace a murine *embryonic stem cell line having a mutation in a gene comprising the nucleotide* sequence disclosed in SEQ ID NO: 294. The instant specification has discussed that such embryonic stem cells can be used for creating transgenic animals, screening assay to identify compounds that may act to ameliorate developmental or cell differentiation disorder systems, gene discovery, and production of mutated proteins. *See pages 11-12 of the specification. However, the evidence of record does not* provide a correlation between the nucleotide sequence set forth in SEQ ID NO: 294 and any gene which comprises the nucleotide sequence set forth in SEQ ID NO: 294 or protein product that it encodes. Moreover, while the specification has purported that the nucleotide sequence set forth in SEQ ID NO: 294 is contained within a gene, the *specification has not disclosed which gene may contain said nucleotide sequence or* which protein (and its function) is encoded by such a gene. In addition, the

specification has failed to establish a relationship between the polynucleotide of SEQ ID NO: 294 and any specific disease or establish any involvement of the polynucleotide of SEQ ID NO: 294 in the etiology of any specific disease. Since SEQ ID NO: 294 lacks a correlation to any known gene or disease it would not be possible to predict a phenotype related to a transgenic mouse comprising a disruption in a gene comprising SEQ ID NO: 294.

A substantial utility is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities under §101. Applicant's specification fails to provide a "real world" use of a gene that comprises the nucleotide sequence set forth in SEQ ID NO: 294 such that the a murine embryonic stem cell comprising a disruption in such a gene additionally has no "real world" use. Neither the specification as filed, nor any art of record disclose or suggest any biological or biochemical activity for the protein encoded by such a gene such that any utility would be well established for the protein. The asserted utilities for SEQ ID NO: 294 such as a probe for diagnosing a disease, primers for PCR, treatment of disease, identification of coding sequences, creation of transgenic animals, production of proteins are merely "potential" uses that apply to any uncharacterized, unrelated polynucleotide sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO: 294. As such an unidentified gene comprising the nucleotide sequence of SEQ ID NO: 294 or a murine ES cell comprising a disruption in such an identified gene also lack specific utilities.

The asserted utility of a murine ES cell comprising a disruption in a gene containing SEQ ID NO: 294 is based on the assertion that SEQ ID NO: 294 is a part of a gene. The specification has not provided any information regarding which gene may contain SEQ ID NO: 294, which protein (and its function) is encoded by the gene or which disease is related to SEQ ID NO: 294. As such a specific and substantial utility for SEQ ID NO: 294 has not been provided by the evidence of record. Accordingly, an ES cell comprising a disruption in a gene containing SEQ ID NO: 294 also lacks a specific and substantial utility. Finally, a transgenic mouse comprising an ES cell that comprises a disruption in a gene containing SEQ ID NO: 294 would have not any apparent or predictable phenotype since the function of the protein encoded by such a gene is unknown. In the absence of any apparent phenotype, a transgenic mouse would have no obvious utility that is substantial and specific.

In view of the above it appears that the he specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the nucleotide sequence set forth in SEQ ID NO: 294 and murine ES cells comprising a disruption in SEQ ID NO: 294. In view of the lack of guidance with respect to the gene containing SEQ ID NO: 294, the claimed invention encompasses, the skilled artisan would not know how to use such a gene, its expression product, a murine ES cell comprising a disruption in such a gene, or a transgenic mouse comprising such an ES cell. Because the claimed invention as a whole is not supported by a specific and substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claims 1-7 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition to the above issues, the claims as written are subject to an additional enablement rejection as set forth below.

The claims embrace murine ES cells comprising a mutation is a gene comprising the nucleotide sequence set forth in SEQ ID NO: 294. The term murine encompasses animals other than mice, such as rats. The specification has contemplated that such ES cells may be used to create transgenic animals. See pages 11-12. Currently, the state of the transgenic art regarding ES cell technology for the production of transgenic animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al. (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). The state of the art does not support the use of rat embryonic stem cells for creating knockout rats.

Furthermore, the instant specification has failed to provide guidance correlating to the use of non-mouse ES cells.

Given the unpredictable and undeveloped state of the ES cells art it would have required undue experimentation for the skilled artisan to create transgenic knockout of murine species other than mouse.

Claim 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a genetically engineered mammalian cell comprising a recombinant polynucleotide inserted into a gene comprising the nucleotide sequence set forth in SEQ ID NO: 294. The claims are further directed to a murine embryonic stem cell line comprising a retroviral gene trap vector in a gene comprising the nucleotide sequence set forth in SEQ ID NO: 294.

The genes comprising the nucleotide sequence set forth in SEQ ID NO: 294 encompassed within the genus have not been disclosed. Based upon the prior art there is expected to be variation among the species of genes within the genus, because the gene species would be expected to vary among individuals. The specification discloses isolation of a nucleotide sequence (SEQ ID NO: 294) from mouse ES cells and purports

that SEQ ID NO: 294 is part of the coding sequence from a gene. There is no evidence on the record of a relationship between the structure of any gene and the sequence set forth in SEQ ID NO: 294 that would provide any reliable information about the structure of any gene within the genus. There is no evidence on the record that the nucleotide sequence set forth in SEQ ID NO: 294 had a known structural relationship to any gene sequence. Moreover, the structural elements of a gene comprising SEQ ID NO: 294 such as regulatory regions, intron-exon boundaries, and 3' regions have not been disclosed. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because partial coding sequence as set forth in SEQ ID NO: 294 is not representative of any gene within the claimed genus. Consequently, since Applicant was in possession of only a partial coding sequence of a gene, the nucleotide sequence set forth in SEQ ID NO: 294 was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of gene comprising the nucleotide sequence set forth in SEQ ID NO: 294 as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 7 are indefinite as written because the specification has not provided a definition for a gene which comprises the nucleotide sequence set forth in SEQ ID NO: 294. The elements, which define a gene such as regulatory regions, intron-exon boundaries, and 3' regions have not been defined by the instant specification. Claims 2-6 depend from claim 1. Appropriate correction is required.

Claim 1 is indefinite as written. The claim embraces a gene identifiable as corresponding to SEQ ID NO: 294. The claim is indefinite as written because it is not clear how a gene corresponds to the nucleotide sequence set forth in SEQ ID NO: 294. The specification has alleged the nucleotide sequence of SEQ ID NO: 294 is a partial sequence of an unknown gene. Claims 2-6 depend from claim 1. Appropriate correction is required.

Claim 7 is indefinite as written. The claim embraces a gene comprising a polynucleotide sequence identifiable as encoding SEQ ID NO: 294. As set forth in the sequence listing provided by the instant specification, the sequence contained within SEQ ID NO: 294 is nucleotide. The claim is indefinite as written because it is not

known how a gene can encode a nucleotide sequence. Genes are known to encode polypeptides. Appropriate correction is required.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.
Art Unit 1632

PETER PARAS
PATENT EXAMINER